

REMARKS

Applicants acknowledge that the Examiner has found their previous arguments (timely filed on August 4, 2004) against restriction of the subject matter of Groups I and II persuasive, and has rejoined the claims of these two Groups, and withdrawn the requirement for a species election, in the present application. Claims 1, 17-20, 22, and 27-45 have been withdrawn, and claims 5-10 have been canceled. Claims 2-4, 11-16, 21, and 23-26 are presently pending.

Claims 11-13, and 24-25 have presently been amended to remove certain subject matter (directed to “protein-protein binding motifs”) not elected by Applicants in response to the previous Restriction Requirement. In their response to the Restriction Requirement, Applicants indicated such non-elected subject matter would be removed from claims 11-13 and 24-25 upon the present rejoinder of the subject matter of Groups I and II. Applicants reserve the right to pursue such subject matter in a later divisional or continuation filing.

Claim 21 has presently been voluntarily amended to more distinctly point out the characteristics and features of the claimed subject matter. More particularly, claim 21 has been amended to clarify that the claimed antibody specifically binds a motif that “consists of” the structural elements recited in subparts (i) and (ii), rather than merely “comprising” those elements. This amendment clarifies the “motif-specific” and “context-independent” characteristics of the claimed genus of antibodies, as described in detail throughout the specification. Claim 21 has also been amended to recite that the claimed antibody binds a plurality of “non-homologous” peptides or proteins within an organism. This amendment clarifies that the “context-independent” characteristic of the claimed antibody lies in its ability to bind the recurring motif for which it is specific in many *different* proteins within an organism, rather than merely binding an epitope that is highly or entirely conserved among isoforms (homologues) of the *same* protein. These amendments are supported throughout the specification as originally filed, for example, at p. 6, lines 20-27; p. 15, lines 8-19; p. 24, line 14 to p. 25, line 24; p. 26, line 25 to p. 27, line 24; p. 28, lines 8-28; p. 31, lines 1-17; and Figures 2-4 and 6-29 (*see* Brief Description of Drawings, pgs. 8-12). The present amendments do not introduce new matter.

OBJECTION, UPDATED PRIORITY STATUSES

The Examiner has objected to the specification for failing to recite the updated statuses of the related applications to which priority is claimed.

Applicants have presently amended the “Related Applications” section of the specification (on page 1, at lines 3-7) as filed to recite the updated statuses of the priority applications. MPEP §201.11(E). Accordingly, Applicants respectfully request that this objection be withdrawn.

OBJECTION, NON-ELECTED INVENTIONS

The Examiner has objected to claims 11-13, and 24-25 for being drawn, in part, to inventions not elected by Applicants in their previous response to the Restriction Requirement dated June 8, 2004. In that response and request for reconsideration, Applicants indicated that certain non-elected subject matter would be removed from these claims upon the present rejoinder of the subject matter of Groups I and II.

Applicants have now presently amended claims 11-13, and 24-25, to remove the non-elected subject matter objected to by the Examiner. More specifically, these claims have been amended to remove preferred certain subject matter directed to “protein-protein binding motifs.” Accordingly, Applicants respectfully request that this objection be withdrawn. Applicants reserve the right to pursue this and other non-elected subject matter in later divisional or continuation filing.

§102(B) NOVELTY REJECTIONS

The Examiner has rejected claims 21 and 23 under 35 U.S.C. §102(b) as allegedly being anticipated by Mandelkow *et al.* (EP 544,942, “Novel Tools for the Diagnosis and Treatment of Alzheimer’s Disease” (published June 9, 1993)) (hereinafter “Mandelkow”), as evidenced by Paul, FUNDAMENTAL IMMUNOLOGY (text), 1993 Ed., pp. 242-243 (hereinafter “Paul”). The Examiner asserts that Mandelkow discloses two Tau-specific phospho-epitope antibodies (SMI33 and SMI34) that fall within the scope of the present claims since they bind the epitope in multiple isoforms of Tau. While noting that Mandelkow *fails* to disclose the particular size/structure of the epitope bound by the cited antibodies, the Examiner argues that the size/structure can be inferred to be within the scope of the present claims based on the disclosure of Paul, hence claims 21 and 23 are not novel over Mandelkow in view of Paul.

Applicants respectfully disagree. As discussed below, the cited antibodies disclosed in Mandelkow are no more than traditional site-specific antibodies, one of which (SMI33) does not bind a phosphorylated epitope, the other of which (SMI34) has unknown binding specificity, and both of which merely cross-react with a highly conserved region within isoforms of the same protein (Tau).

Accordingly, the antibodies disclosed in Mandelkow fail to meet each and every limitation of the presently claimed subject matter, hence the cited reference (regardless of Paul) fails to anticipate the invention of claims 21 and/or 23.

Motif-Specific, Context-Independent Antibodies are Distinct from Site-Specific Antibodies.

In order to assist the Examiner in better understanding the features of the subject matter (a novel genus of antibodies) of claims 21 and 23, Applicants here briefly summarize and distinguish the binding specificity, characteristics and features of the presently claimed class of antibodies from those of prior art "site-specific" or "epitope-specific" antibodies -- such as those disclosed in Mandelkow -- which lack these novel and unique characteristics.

As discussed in the Background section of the present application, there was, at the time the instant application was filed, an unmet need for a new type of antibody that would be capable not only of *specifically binding* a short, modified (e.g. phosphorylated) and recurring sequence motif, but would also be capable of binding it in *many different* proteins from an organism in which it recurred. Antibodies with such binding characteristics were envisioned to be highly useful and necessary for researching signal transduction pathways, where such short modified, recurring sequence motifs were known to be central to propagation of an intracellular signal among different proteins involved the signaling cascade. *See, e.g.* Background at page 1, lines 6-21. However, antibodies with such binding characteristics were not yet available and, therefore, research efforts had been limited and burdened by the necessity to use many different antibodies each essentially capable of specifically binding only a single protein or phosphorylation site (or epitope) against which they were designed to be specific. Although the production and use of such site-specific antibodies, including phosphorylation-site specific antibodies, was well known and developed in the art (*see, e.g.* Czernik, cited in Background of the specification), the usefulness of these antibodies in examining signal transduction across multiple different signaling proteins remained limited.

The present inventors overcame the limitations of prior art site-specific antibodies by providing, for the first time, a novel class of antibodies having the desired binding features of motif-specificity (the ability to *specifically bind* short, recurring sequences motifs relevant to signal transduction processes – as opposed to binding a larger epitope which contained such a motif) and context-independence (the ability to bind *the motif* in many *different* proteins within an organism in which it recurs – as opposed to merely binding a unique epitope in a single target protein or homologues of that protein having a conserved and identical or nearly identical epitope).

Prior art site-specific antibodies produced by the standard anti-peptide production methodologies (such as those disclosed in Mandelkow) *do not* have the binding specificity and

characteristics of the presently claimed class of antibodies. Rather, site-specific antibodies are typically raised against – and are specific for – unique, longer sequences (or epitopes) that occur in a single protein of interest (which may be highly conserved among isoforms/homologues of the *same* protein). Often, the precise sequence of the epitope bound by a site-specific antibody is not even known. Site-specific antibodies, therefore, do not *specifically bind* a short recurring motif, such as a kinase consensus substrate motif, and are *not* capable of binding it in multiple *different* proteins (*i.e.* not homologues or isoforms of the same protein) that contain the recurring motif, within the scope of the present invention. Accordingly, the binding characteristics and specificity of traditional site-specific antibodies is distinguished from the presently disclosed and claimed class of motif-specific, context-independent antibodies.

The powerful and novel class of antibodies provided by the invention enable, for the first time, the ability to simultaneously examine the modification statuses of multiple *different* signaling proteins (containing a common, recurring modified motif) from an organism using a single antibody, and are changing the face of signal transduction research. For example, a single antibody of the invention can be used to profile many, if not all, proteins across the proteome of an organism that contain a target phosphorylated motif. Among such antibodies are the preferred genus of kinase consensus substrate motif-specific antibodies presently claimed in dependent claim 23 (as well as the non-elected, preferred genus of protein-protein binding motif-specific antibodies); unique antibodies, that, until the time of the present invention, were not available.

The Cited Antibodies Fail to Anticipate the Claimed Subject Matter.

In contrast to the novel antibodies of the present invention,, the SMI33 and SMI34 antibodies disclosed in Mandelkow are merely traditional phosphorylation site-specific antibodies that bind the Tau protein (and its various isoforms), only when phosphorylated – or not phosphorylated -- at a particular epitope on Tau (which is conserved among the Tau isoforms). Mandelkow itself, entitled “Novel Tools for the Diagnosis and Treatment of Alzheimer’s Disease,” is concerned with identifying a protein phosphorylation site/epitope unique to Alzheimer’s patients in order to provide diagnostic tools for the disease. A variety of commercially available Tau-specific antibodies, including SMI33 and SMI34, were employed in the studies disclosed in Mandelkow in an attempt to identify such a unique epitope.

The cited SMI33 and SMI34 monoclonal antibodies are, however, readily distinguished from the class of motif-specific, context-independent antibodies presently claimed on several grounds. Both the SMI33 and SMI34 monoclonal antibodies utilized in Mandelkow are commercially available from Sternberger Monoclonals, Inc. (see <http://home.att.net/~sternbmonoc/home.html>). The product literature for SMI33 indicates that this antibody reacts only with a non-phosphorylated Tau

epitope, which is also confirmed in Mandelkow itself (*see, e.g.* Fig. 16 lane (b), page 9, lines 30-35). The precise epitope/sequence for which SMI33 is specific is stated to be unknown. Indeed, a more precise study utilizing these two antibodies, Lichtenberg-Kraag *et al.*, *Proc. Natl. Acad. Sci. USA* 89: 5384-5388 (June 1992) (Ref. CZ), confirmed that SMI33 binds a non-phosphorylated epitope, and that the particular specificity of this antibody, while in the region of the first Lys-Ser-Pro sequence (residues 234-236), is unknown (*see* Lichtenberg-Kraag, *e.g.*, at p. 5386). Accordingly, the cited SMI33 antibody fails to meet each and every limitation of claim 21 since it is *not* specific for a phosphorylated motif, its binding specificity is unknown, and further since it is not disclosed as binding a motif which in fact recurs in multiple different proteins (rather, it binds a unique epitope in a single protein, Tau, which is conserved in all isoforms of this protein (*see* Lichtenberg-Kraag at p. 5386, column 1, second paragraph)). Similarly, the cited SMI33 antibody is not disclosed as specifically binding a kinase consensus substrate motif (rather, SMI33 binds an unspecified epitope that may *contain* a motif that is itself is phosphorylated by a kinase). Thus, SMI33 further fails to meet each and every limitation of dependent claim 23.

Similarly, the cited SMI34 antibody disclosed in Mandelkow also fails to anticipate the presently claimed subject matter since it does not meet each and every limitation of the claims. SMI34 is disclosed (both in Mandelkow and in the product literature available from Sternberger Monoclonals, Inc. (*see* website above)), as binding an epitope of Tau only when phosphorylated. In that respect, this antibody is a phosphorylation-site specific antibody. However, Mandelkow itself clearly states, in its Background section discussing the limitations of prior art antibodies like SMI34, that the precise epitope for which this antibody is specific is *unknown* (*see* Mandelkow at p. 2, lines 46-52). The binding experiments reported in Mandelkow further underscored that the precise epitope (and required residues) bound by SMI34 are unknown, but that its binding specificity is “complex” and was concluded to be conformation-dependent and involving contact with sequences outside of the phosphorylation site. *See* Mandelkow, p. 14, lines 55-58; p. 15, lines 24-39 (and Table 1). Indeed, the conformation-dependent binding of this antibody necessarily requires that the epitope be presented in the correct “context” of the Tau sequence, underscoring that it is not a “context-independent” antibody like those of the present invention.

In fact, the Mandelkow authors, in a related publication (*see* Lichtenberg-Kraag (1992), *supra*, at p.5387, second column, third paragraph) disclosed that the “search for the SMI34 epitope leads to an apparent contradiction” and went on to “hypothesize” about a variety of factors involved in the complex binding characteristics of the antibody. This uncertainty was underscored by a later publication (Poulter *et al.*, *J. Biol. Chem.* 268: 9636-9644 (1993) (Ref. CAA), which, in examining epitope specificity of SMI34, concluded that antibody did not even bind the epitope originally assumed and that specificity remained unresolved. *See* Poulter at, *e.g.*, p. 9641, second column

“Discussion” and p. 9644, last paragraph. None of these references, including Mandelkow, discloses, in any way, that the precise epitope for which SMI34 is specific is a kinase consensus substrate motif (or a protein-protein binding motif, for that matter).

Accordingly, the SMI34 antibody disclosed in Mandelkow fails to meet each and every element of claims 21 and 23, since it does not *specifically bind a motif* that comprises (or consists of) two to six invariant amino acids. Indeed, the precise specificity of the SMI34 is not known, nor disclosed in Mandelkow, and is not identified as being a kinase consensus substrate motif, much less any other short, non-unique motif that recurs in unrelated proteins.¹ Further, SMI34 is not disclosed of being able to specifically bind such a motif in a plurality of different peptides or proteins in which the motif recurs. Rather, SMI34 merely binds an epitope that is highly conserved, if not identical, in the six isoforms of the same protein, Tau (*see* Lichtenberg-Kraag, *supra*., at p. 5386, column 1, “Antibody Epitopes”, first paragraph). SMI34 is no more than a traditional, phosphorylation-site specific antibody than binds an unresolved, conformation-dependent epitope conserved among the six homologous forms of Tau. It does not have the characteristics and features of the presently claimed class of motif-specific, context-independent antibodies, and thus fails to anticipate the present claims.

The failure of Mandelkow to disclose an antibody that *specifically binds* a recurring phosphorylated motif having the structural elements recited in present claims is in no way cured by the disclosure of Paul. The disclosure of Paul (a general textbook relating to immunology) cited and relied on by the Examiner occurs in short section of the book entitled “Protein and Polypeptide Antigen Determinants.” In that section, Paul discusses the nature of peptide antigen contact with the antibody combining site, within which certain residues of the antibody make contact with certain residues of the antigen. In discussing the size of the antibody combining site itself, Paul cites three studies from the mid-to-late 1960’s (Schlossman *et al.*, *Biochem.* 4: 1638-1645 (1965); Schlossman *et al.*, *J. Immunol.* 99: 111-114 (1967); and Van Vunakis *et al.*, *Immunochem.* 3: 393-402 (1966)), in the early days of antigen-antibody research, which indicated that – in the case of short, synthetic, oligopeptide antigens -- the maximum number of antigen residues that could physically fit within the three dimensional space of the antibody combining site cleft was six to eight residues (*see* Paul at p. 243, first paragraph). In discussing and citing these studies, however, Paul does *not* disclose or suggest that every epitope bound by an antibody is inherently six to eight residues in size. Rather, the disclosure of Paul is limited to teaching that six to eight residues is the maximum number of

¹ The Examiner has acknowledged the same on page 3, lines 5-7 of the October 20, 2004 Office Action, but argues that another general reference, Paul (1993), cures the deficiencies of Mandelkow by teaching that a typical epitope is six residues long. This is, in fact, not the case, and the limited teachings of Paul are discussed, and distinguished, below.

olopeptide residues that can fit within the three dimensional space of the antibody combining site. Paul does not teach that epitopes cannot be larger, and that other epitope contacts outside the combining site are not critical to antibody binding specificity. In fact, later studies on antibody binding specificity established just that, and the more modern view that there is no magic or general number of residues involved in epitopic binding specificity for a particular antibody was established.²

This modern view is highlighted by definitive texts in the field of immunology and antibody use, such as **USING ANTIBODIES: A LABORATORY MANUAL**, Harlow & Lane, Cold Spring Harbor Laboratory Press (1999) (Ref. CAC). In discussing the size and nature of protein epitopes (at p. 25 in the chapter titled “Structure of the Antibody-Antigen Complex”), **ANTIBODIES** teaches that, while early studies had indicated the antibody combining site cleft was relatively small, epitopes bound by antibodies can, in fact, be quite large and can involve multiple contacts with several or all of the CDRs of an antibody. *See ANTIBODIES* p. 25. Indeed, the text discusses, as an example, an epitope on lysozyme that consists of 16 amino acids from two distant regions of the protein. While noting that some antibodies can recognize epitopes that are quite large, **ANTIBODIES** notes that certain epitopes bound by other antibodies can be quite small, as is the case with a single phospho-residue. The same distinction is made in another modern text, **IMMUNOLOGY**, J. Kuby, 3rd Ed. (1998), Freeman & Co. (Ref. CAD), which teaches that while small peptide antigens may bind within an antibody combining site cleft, the same does not hold true for larger epitopes on protein. *See IMMUNOLOGY*, p. 93. Accordingly, there is no set number of residues that is recognized in the art as comprising a particular or “typical” epitope. Rather, those of skill in the art appreciate that the size of a particular epitope for which a particular antibody is specific will depend on a number of factors, including the size and nature of the protein or peptide in which the epitope occurs, presence of hydrophilic/phobic residues, conformation-dependent interactions, and potential involvement of more distant interacting domains on the protein.

Accordingly, one of ordinary skill in the art of antibody production and use (to which the present invention relates) would in no way conclude – based on the disclosure of Paul -- that the epitope for which SMI34 is specific comprises (or consists of) just six amino acids. In fact, as discussed above, skilled artisans in the field trying to establish the epitopic specificity of SMI34 expressly concluded that the precise specificity is unknown, and involved residues other than the putative phospho-epitope that were causing conformation dependent binding. *See* Lichtenberg-Kraag, *supra.*; Poulter, *supra.*; Mandelkow, *supra*. In sum, Mandelkow (even in view of Paul) utterly

² For example, in a later review entitled “The Antibody Combining Site,” Capra *et al*, *Sci. Am.* 236: 50-59 (1977) (Ref. CAB), it was noted that the binding of a small synthetic antigen to a crystallized antibody is a “highly artificial situation” and that in real life, larger, three dimensional protein epitopes likely bind the antibody not only, in part, in the combining site itself, but around and outside it as well. *See supra.* at p. 58, center paragraph.

fails to disclose an antibody that meets each and every element of motif-specificity and context-independent binding recited in claims 21 and 23. Accordingly, the presently claimed invention is novel over Mandelkow (regardless of Paul), and Applicants respectfully request that this rejection be withdrawn.

The above distinctions notwithstanding, Applicants have presently voluntarily amended claim 21 to more distinctly point out the features and characteristics of the claimed subject matter. More particularly, claim 21 has been amended to clarify that the claimed antibody specifically binds a motif “consisting of” the recited structural elements rather than merely “comprising” such elements. This amendment clarifies an important characteristic of the antibodies of the invention that is described throughout the specification: they specifically bind their target motif, rather than merely binding a larger epitope that happens to comprise such a motif (as is the case with the antibodies disclosed in Mandelkow). This characteristic of the antibodies of the invention enables them to bind their target motif in a multitude of *different* protein contexts in which the motif is presented, and makes them suitable, *e.g.* for proteome-wide profiling using a single antibody. This amendment is supported throughout the specification as originally filed, *e.g.* at p. 6, lines 20-27; p. 15, lines 8-19; p. 24, line 14 to p. 25, line 24; p. 26, line 25 to p. 27, line 24; p. 28, lines 8-28; p. 31, lines 1-17; and Figures 2-4 and 6-29 (see Brief Description of Drawings, pgs. 8-12), and does not introduce new matter.

Claim 21 has also been voluntarily amended to clarify that the claimed antibody specifically binds the target motif in a plurality of “non-homologous” peptides or proteins in which it recurs. The amendment clarifies an important characteristic and feature of the antibodies of the invention that is described throughout the specification: they are designed to, and are capable of, binding the motif for which they are specific in a multitude of *different* proteins (or peptides) in which the motif recurs within an organism. This powerful characteristic of the antibodies of the invention makes them highly useful for, *e.g.* detecting many different and unrelated proteins (*i.e.* non-homologous proteins) within an organism that contain the phosphorylated target motif (*e.g.*, a MAPK consensus substrate motif), using only a single antibody. In contrast, a site-specific antibody that merely recognizes a unique epitope that happens to be highly conserved, if not identical, among isoforms/homologues of the *same* protein is not capable of doing the same (as is the case with the antibodies disclosed in Mandelkow). This amendment is supported throughout the specification as originally filed, *e.g.* at p. 6, lines 20-27; p. 15, lines 8-19; p. 24, line 14 to p. 25, line 24; p. 26, line 25 to p. 27, line 24; p. 28, lines 8-28; p. 31, lines 1-17; and Figures 2-4 and 6-29 (see Brief Description of Drawings, pgs. 8-12), and does not introduce new matter.

§103(A) OBVIOUSNESS REJECTIONS

The Examiner has rejected claims 2-4, 11, 21, and 23 under 35 U.S.C. §103(a) as allegedly being obvious given Mandelkow (EP 544,942; *see supra*) in view of Paul (1993; *see supra*) and in further view of Pinilla *et al.*, *Peptide Research* 8: 250-257 (1995) (hereinafter “Pinilla”).³ The Examiner asserts that, since Mandelkow discloses certain peptide epitopes on Tau that comprise a Ser-Pro or Thr-Pro “motif,” and since Pinilla teach the use of combinatorial peptide libraries to characterize antibody binding specificity, that it would have been *prima facie* obvious for a skilled artisan to employ the techniques of Pinilla to screen for an antibody having specificity for the “motif” disclosed in Mandelkow, thereby rendering the presently claimed subject matter obvious.

Applicants respectfully disagree, and submit that the Examiner has failed to establish a *prima facie* case of obviousness over the cited references. As discussed in more detail below, the cited references, whether in combination or taken alone, not only fail to teach each and every limitation of the presently claimed subject matter, but also fail to provide any suggestion or motivation for their combination or expectation that such combination would yield success. Accordingly, the subject matter of claims 2-4, 11, 21, and 23, is non-obvious and patentable over Mandelkow and Pinilla (regardless of Paul).

It is well established that, in order to meet his/her initial burden of proof in establishing a *prima facie* case of obviousness, an Examiner must establish three elements: (i) that there is some suggestion or motivation in the references themselves – or if not, then in the knowledge generally available to those of skill in the art – to combine the teachings of the references; (ii) that there is some reasonable expectation of success, as evidenced by the cited references and/or other prior art, in so combining the teachings, and (iii) that the cited references teach or suggest each and every limitation of the claimed subject matter. *See* MPEP §§2142, 2143, *citing*, e.g. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). In establishing the above criteria, a general allegation of level of skill in the art *cannot* be relied on to provide a suggestion to combine teachings (*see* MPEP §2143.01, *citing* *Al-Site Corp v. VSI Int'l.*, 174 F.3d 1308) (Fed. Cir. 1999)), and the mere fact that references can be combined is *not* sufficient to establish desirability or motivation to do so (*see* MPEP §2143.01, *citing* *In re Mills*, 916 F.2d 680) (Fed. Cir. 1990)).

In the present case, a *prima facie* case of obviousness has not been established because each of the three required elements has not been met. The present invention pertains to the provision of a novel class of antibodies that are designed to, and capable of, specifically bind(ing) short, recurring modified motifs irrespective of the context in which the motif occurs across a multitude of different

proteins, and to the development of a reproducible method for generating such antibodies. In contrast, the problem to be solved in Mandelkow was identifying a phosphorylated protein epitope unique to Alzheimer's patients that could then be used for diagnostic purposes. Similarly in contrast, the problem to be solved in Pinilla was to provide a method for examining the cross-reactivity and specificity of an antibody with respect to its antigen. Neither Mandelkow nor Pinilla is directed to, nor renders obvious, the creation of a novel class of antibodies that are both motif-specific, and context-independent, or to developing a reproducible method of generating such novel antibodies.

There is No Motivation or Suggestion to Combine the Teachings of Mandelkow & Pinilla.

As noted by the Examiner, Mandelkow discloses 21 different Tau-derived peptide sequences, each of which contains at least one phosphorylatable serine or threonine residue, which are disclosed as being unique to Alzheimer's patients. (See Mandelkow, Sequence Listing at p. 16). Although Mandelkow discloses that each of these sequences contains a Ser-Pro or Thr-Pro motif (some contain both (see e.g. SEQ ID NOs: 4 and 10), the epitope sequences themselves range from 6 residues long to 12 residues long, differ in actual composition, and correspond to entirely different regions of Tau (e.g. some correspond to the region of residues 43-54, while others correspond to the region of residues 419-425 in the Tau sequence). While Mandelkow suggests that site-specific antibodies against each of these 21 different epitopes would be useful as Alzheimer's diagnostic reagents, there is simply no teaching, suggestion, or motivation provided in Mandelkow to create a single antibody that can specifically bind a Ser-Pro or Thr-Pro motif itself without regard to surrounding epitope sequence, much less how to actually generate such an antibody. Indeed, as discussed in detail earlier in this Response, Mandelkow itself, in identifying the 21 Tau epitopes specific to Alzheimer's disease, utilized and described site-specific antibodies whose precise binding specificity is unknown. Mandelkow expressly acknowledges that the epitopic specificity of the antibodies it suggests for diagnostics (and claims) is unknown by stating that the epitope may comprise some or all of any of the 21 disclosed epitopes, one or more phosphorylated serines or threonines or both, and that some of the residues in each epitope may not, in fact, contribute to the specificity of the antibody. See Mandelkow, e.g. at p. 3, lines 28-50).

In short, Mandelkow fails to provide any teaching or suggestion of a motif-specific, context-independent antibody as presently claimed, much less teaching or suggesting a reproducible method for how to create such a unique antibody. The Examiner notes as much in stating that "Mandelkow do not teach a method for making a motif-specific, context-independent antibody which would bind to all of the [21 disclosed epitopes] when T or S where phosphorylated" (See October 20, 2004

³ Applicants note that subject matter of the claims of the present application, as well as that of the priority applications to which benefit is claimed, was and is commonly owned by CELL SIGNALING TECHNOLOGY, INC.,

Office Action at p. 4, third paragraph). Rather, Mandelkow merely discloses the desirability of generating epitope-specific antibodies, by standard, prior art methods, that can bind any one of the 21 distinct phosphorylatable epitopes identified as useful for Alzheimer's diagnosis. In no way, however, does Mandelkow teach, suggest, or make obvious, how to create a single antibody that would be capable of specifically binding only the phosphorylated Ser-Pro or Thr-Pro motif that is comprised in each of the 21 disclosed epitopes. Indeed, the creation of antibody with such characteristics and features remained an unsolved problem in the art until the present inventors solved it.

The deficiencies of Mandelkow are in no way cured by Pinilla, which, whether taken alone or in combination with Mandelkow, similarly fails to teach, suggest, or motivate the creation of a unique class of motif-specific, context-independent antibodies, as presently claimed. Pinilla is concerned with using a combinatorial peptide library of hexapeptides to characterize the required/preferred antigen residues for which a monoclonal antibody (Mab 222-35C8) is specific. The single Mab studied in Pinilla was raised, according to standard prior art anti-peptide antibody production techniques, against a 14 amino acid synthetic peptide antigen, LHNNEAGRTTVFSC, corresponding to an unphosphorylated epitope on oncogene related protein *int-1* (see Pinilla at p. 251, first column). Pinilla discloses that examination of the specificity of Mab 222-35C8 for its antigenic determinant, GRTTVFS (itself only a portion of the larger epitope used to raise the Mab), using the combinatorial hexapeptide library reveals that certain residues can be changed and still retain the antibody recognition, albeit it with several-fold increase, or decrease, in the affinity. For example, Pinilla discloses that changing the first threonine to tyrosine increased the binding specificity of the Mab (see Pinilla at p. 255, second column). Pinilla concludes by suggesting that the combinatorial peptide approach employed with Mab 222-35C8 might also be employed more generally as a technique to study the precise binding requirements and tolerated variability (or "polyspecificity") of a particular antibody for its epitope. At the same time, however, Pinilla expressly notes that the specificity of the examined Mab for different hexapeptide scaffolds used in the study appeared to be different, and likely depended on factors such length of the antigen itself and secondary structure (see Pinilla at p. 256, first paragraph of columns one and two, and last paragraph of column 3).

Thus, while Pinilla suggests a general approach to characterizing the polyspecificity of a given epitope-specific antibody, it simply fails to teach, suggest, or provide motivation for how to create a motif-specific, context-independent antibody within the scope of the present invention. Rather, the teaching of Pinilla is limited to how to characterize the binding specificity of prior art epitope or site-specific antibodies using artificially created hexapeptides that do not represent a

motif that naturally recurs across different proteins in an organism. There is no suggestion or motivation provided in either Pinilla or Mandelkow to attempt to characterize the precise polyspecificity of the Tau-specific antibodies disclosed in Mandelkow using the approach disclosed in Pinilla (in fact, the Mandelkow authors, and well as later studies, failed to ever employ such an approach to figure out the specificity of the Tau-specific antibodies (*see* earlier discussion; Lichtenberg-Kraag, *supra.*; Poulter, *supra.*)). However, were one of skill in the art to so combine the limited teachings of Mandelkow and Pinilla, the references together would still completely fail to teach, suggest, or provide motivation for the inventive approach employed by the present inventors in creating a novel class of motif-specific, context-independent antibodies, which have characteristics and features not met by prior art antibodies of the type disclosed in the cited references.⁴

Accordingly, the Examiner has failed to establish the first required prong of *a prima facie* showing of obviousness, and the present rejection of claims 2-4, 11, and 21-23 should, respectfully, be withdrawn. MPEP §§2142, 2143.01.

The Skilled Artisan Would Have No Expectation of Success in Combining Mandelkow & Pinilla to Create a Motif-Specific, Context-Independent Antibody.

As noted above, there is no teaching, suggestion, or motivation to combine the disclosures of Mandelkow & Pinilla, and the mere fact that they *can* be combined does not establish motivation to do so. However, even if one of skill in the art *were* to so combine their teachings, there would be absolutely no expectation of success (much less a reasonable one) in isolating or producing a motif-specific, context-independent antibody as presently claimed. Assuming, arguendo, that a skilled artisan motivated to determine the polyspecificity of the Tau-specific antibodies suggested in Mandelkow decided to apply the combinatorial hexapeptide library screening approach disclosed in Pinilla, the only reasonable expectation of success such artisan would have would be in determining the particular residues of each of the 21 Tau epitopes disclosed in Mandelkow that are preferred/required by a site-specific antibody that binds one of such epitopes. Such an artisan would simply have no expectation whatsoever, based on the teachings of Mandelkow and Pinilla (or any other knowledge in the art), that such an approach would successfully isolate, or produce, an antibody capable of *specifically* binding a short, recurring phosphorylated motif in a context-independent manner as presently claimed.

At best such an artisan (were there some suggestion or motivation to combine the teachings

⁴ Paul fails to cure the deficiencies of Mandelkow and Pinilla, in combination or alone. There is simply no teaching, suggestion, or motivation provided by Paul to combine its limited teachings, with or without the method

of Pinilla and Mandelkow) might reasonably expect to characterize the polyspecificity of a Mandelkow-suggested Tau-specific antibody for an epitope that happens to comprise two residues (Ser-Pro or Thr-Pro) that might, taken alone, itself be considered a motif. However, attempting to randomly isolate a motif-specific antibody, context-independent antibody specific for such a two-residue motif that happens to be comprised within one or more of the 21 Tau epitopes disclosed in Mandelkow by employing the approach of Pinilla would amount to no more than a fishing expedition with little expectation of success. The combined teachings of Mandelkow and Pinilla utterly fail to provide any teaching or suggestion of how to isolate or create such a novel antibody. Indeed, as discussed in the Background of the present specification, prior art attempts to create the presently claimed class of antibody had failed, and such antibodies simply were unavailable until the time they were first provided by the present invention.

Accordingly, the Examiner has failed to establish the second required prong of *a prima facie* showing of obviousness, and the present rejection of claims 2-4, 11, and 21-23 should, respectfully, be withdrawn. MPEP §§2142, 2143.02.

Mandelkow & Pinilla Fail to Teach or Suggest Each and Every Element of the Present Claims.

The third required prong of *a prima facie* showing of obviousness has also not been met because Mandelkow & Pinilla, taken alone or in combination (regardless of Paul), fail to disclose each and every element of the presently claimed subject matter.

Claims 2-4, and 11 are drawn to a method of producing a novel type of antibody (a “motif-specific, context-independent antibody”) that is capable of specifically binding a short, recurring modified motif in a multitude of different peptides or proteins in which the motif recurs. The claimed method requires the construction, and use as an immunogen, of a degenerate peptide library that comprises two distinct structural components: (i) a fixed target motif comprising two to six invariant amino acids and at least one modified amino acid, and optionally, one or more degenerate amino acid positions, and (ii) a plurality of degenerate amino acids that flank the fixed target motif. This novel approach, as discussed in the specification, is based on the inventive concept and surprising discovery that, in order to produce an antibody that is specific for a short (and potentially degenerate) modified motif and will bind it in a multitude of different surrounding peptide/protein contexts, one can use a degenerate peptide library in which only the fixed residues are presented to a host in sufficient concentration to be antigenic. *See, e.g.*, Specification at p. 13, lines 4-23. The method presently claimed further requires the isolation of an antibody that is capable of specifically binding the target motif in a plurality of different protein/peptide contexts in an organism in which it

of polyspecificity screening disclosed in Pinilla, to characterize the epitopic specificity of the Tau-specific antibodies

recurs.

Both Mandelkow and Pinilla fail to teach, suggest, or in any way motivate the creation, and use as an immunogen, of a degenerate peptide library having only a fixed target motif and degenerate surrounding residues, in order to produce a motif-specific, context-independent antibody. Both Mandelkow & Pinilla fail to teach, suggest, or in any way motivate the construction and use of such a degenerate peptide library wherein the fixed target motif is a recurring motif (*i.e.* occurs in multiple different proteins/peptides within the proteome of an organism) comprising (or consisting of) two to six fixed residues including a modified residue, and optionally, one or more degenerate residues contained within the motif. Both Mandelkow & Pinilla fail to teach, suggest, or in any way motivate the isolation of an antibody, or class of antibodies, with the motif-specific and context-independent characteristics and features of the presently claimed class of antibodies. Moreover, neither reference alone or when combined in any way teaches, suggests, or makes obvious a motif-specific, context-independent antibody (or method of producing the same) within the preferred subgroup of antibodies (those specific for kinase consensus substrate motifs) to which dependent claims 11 and 23 are drawn.

Rather, Mandelkow discloses no more than the identification of 21 distinct Tau epitopes that are specific to Alzheimer's disease and have diagnostic utility for the same, and suggests the creation of epitope-specific antibodies to any of these 21 distinct sites. Mandelkow is in no way concerned with, nor teaches or suggests, how to isolate and/or produce a novel class of motif-specific, context-independent antibodies as presently claimed. Pinilla discloses no more than the use of a combinatorial hexapeptide library to characterize the binding preference and polyspecificity of a single monoclonal antibody (raised to a 14-residue protein epitope), and the potential applicability of this approach to characterizing other antibody polyspecificity. Pinilla is in now concerned with, nor teaches or suggests, how to isolate and/or produce a novel class of motif-specific, context-independent antibodies as presently claimed. Indeed, the creation of such a novel class of antibodies was the problem solved by the present invention, and, as discussed in the Background of the present specification, such antibodies, while desired, were unavailable in the art until the time of the present invention.

Accordingly, the Examiner has failed to establish the third required prong of *a prima facie* showing of obviousness, and the present rejection of claims 2-4, 11, and 21-23 should, respectfully, be withdrawn. MPEP §§2142, 2143.03.

In conclusion, Applicants respectfully submit that the Examiner has not met her burden of establishing all of the three required prongs of *a prima facie* showing of obviousness. MPEP §§2142, 2143. The presently rejected claims are non-obvious and patentable over the cited references, and

APPLICANTS: **Comb et al.**
U.S.S.N.: **10/014,485**

the outstanding rejection should, accordingly, be withdrawn.

DOUBLE-PATENTING (NON-STATUTORY) REJECTIONS

The Examiner has rejected claims 2-4, 11-14, and 16 under the judicially-created doctrine of "obviousness-type" double patenting (non-statutory), as allegedly being non-patentably distinct from claims 1-3 and 5 of U.S. Patent No. 6,441,140 (Comb *et al.* -- also owned BY CELL SIGNALING TECHNOLOGY, INC., the assignee of the present application) -- on which priority is presently based in part), in view of Pearson *et al.* (Protein Phosphorylation (1995) (Ref. CX)).

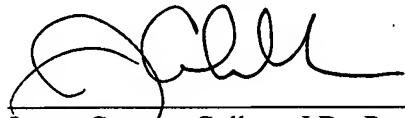
The Examiner has also *provisionally* rejected claims 21, and 23-26 under the judicially-created doctrine of "obviousness-type" double patenting (non-statutory), as allegedly being non-patentably distinct from claims 28-33 and 40-44 of co-pending (allowed) application USSN 09/535,364 (Comb *et al.* -- also owned by CELL SIGNALING TECHNOLOGY, INC., the assignee of the present application -- on which priority is also presently based in part).

While not necessarily agreeing with the Examiner's characterization, Applicants submit herewith a Terminal Disclaimer, in accordance with 37 C.F.R. §1.321(c), to obviate the non-statutory (obviousness-type) double patenting rejections over the cited, commonly owned, issued U.S. patent and pending (allowed) U.S. application. Accordingly, Applicants respectfully request that these rejections be withdrawn.

Conclusion

The present claims are patentable over the prior art, and believed to be in condition for immediate allowance. Reconsideration and withdrawal of the outstanding objections and rejections is respectfully requested, and early and favorable allowance of these claims is earnestly solicited. If there are any questions regarding these amendments and remarks, the Examiner is requested to call the undersigned attorney at the telephone number provided.

Respectfully submitted,



James Gregory Cullem, J.D., Reg. No. 43,569
Intellectual Property Counsel
CELL SIGNALING TECHNOLOGY, INC.
166B Cummings Center
Beverly, MA 01969
(978) 867-2311

3/21/05